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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,399	08/26/2003	Ben-Zion Dolitzky	1662/60903	6089

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EXAMINER	
BERCH, MARK L	
ART UNIT	**PAPER NUMBER**
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/649,399	DOLITZKY ET AL.	
	Examiner	Art Unit	
	/Mark L. Berch/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10,18,19,31,35,37-40,43,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-10,18,19,31,35,37-40,43,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/29/2007 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 35 is rejected under 35 U.S.C. 102(b) as being anticipated by Harnden 1990, with Harnden 1989 supplemental.

In Harnden 1990, see the preparation in the first full paragraph on page 501. The crystallization is done from water. The claims recite among others, methanol/water. However, no limits are set on the ratio of the two solvents; the claim would read on e.g. one part per billion of methanol in water. Even the most tiny trace is enough to qualify (see *SmithKline Beecham Corp. v. Apotex Corp.*, 74 USPQ2d 1398 (CAFC 2005)).

The sentence in which Harnden 1990 reports doing the hydrogenation of the 6-Cl intermediate to obtain the hydrate carries the footnote 8, which conveys that the reaction was done according to the procedure done in footnote 8. Footnote 8 is Harnden 1989. The

hydrogenation of the 6-Cl intermediate does indeed appear in Harnden 1989 as 13 to 14. Therefore, we assume that the procedure used in Harnden 1990 was indeed the procedure used in Harnden 1989. This reaction is done in methanol itself; see paragraph bridging pages 1741-1742. The solvent was removed from the Famciclovir product. However, the solvent removal cannot be exhaustive since it is already known that this compound forms a solvate with methanol. Applicants are reminded that in their example 7, the methanol was retained even though the material was heated for 65°C for 2 hours in a vacuum!! This is probably much more drastic than what Harnden 1989 did, since "solvent removal" does not normally involve such drastic conditions. Therefore the argument that the methanol would be removed in "first solvent removal step in Harnden 1989" is refuted by applicants' own specification. After the solvent is removed, one had a methanol solvate of Famciclovir.

Next, the material is taken up in water and extracted twice with chloroform. Applicants state, "Harnden 1989 discloses a process of preparing famciclovir requiring two steps of solvent removal. Thus, even if one were to assume for argument purposes only that the twice extraction with chloroform may carry several molecules of residual methanol, the residual methanol would have been removed." This misunderstands the process. The extraction with chloroform dissolves in the chloroform both the Famciclovir AND the methanol. As was established by the references cited previously, methanol and chloroform are miscible in all proportions.

Accordingly, when Harnden does the crystallization from water, there are traces of methanol present from the synthesis which were carried along from the chloroform extraction, and therefore the condition of claim 35 are met.

Claims 1-3, 5-10, 18-19, 31, 37-40, 43 are rejected under 35 U.S.C. 102(b) as being anticipated by with Harnden 1989; US 5017701, US 5066805; US 5138057, US 6846927, 6342603, Freerer, Geen, 6437125, and WO 200006573.

In Harnden 1989, note the crystallization of (14) from Ethyl acetate/hexane. In US 5017701, note column 7, line 31, where it is crystallized from hot n-butanol; the same is seen in example II-5 of 6342603. In US 5066805, see Column 3, where the solid appears to be prepared by evaporation from a chloroform/methanol solution. In US 5138057, see Column 8, lines 11-12 and 33, where it was crystallized from Ethyl acetate/diethyl ether and from n-butanol. In 6846927, the product was recrystallized from n-butanol but then reslurried in n-heptane, stirred and filtered, i.e. triturated with n-heptane. In Freerer, the crystallization was done from hot isopropanol; see last example. A similar procedure was done with in example 9 of 6437125. In WO 200006573, see synthesis example 11, which has trituration with diethyl ether. In Brand, see page 5251, with crystallizing from aqueous acetone. In Geen, note 9c, crystallized from n-Butanol.

Insofar as Claim 31 is concerned, the references which recited n-butanol anticipate, and provide further evidence that this is Form II, since the same method is used. Insofar as Claim 18 is concerned, the reference which recites diethyl ether trituration anticipates, and provide further evidence that this is Form I, since the same method is used. Insofar as Claim 30 is concerned, the references which recite isopropanol anticipate, and provide further evidence that this is Form I, since the same method is used.

The traverse is unpersuasive. MPEP 2112 states:

"SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY

The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

In this case, the "unknown property" is the particular crystalline form. This is unknown because the reference is silent on this property. MPEP 2112 goes on to state:

"A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection."

Again, the "CHARACTERISTIC" which the prior art is silent on is the crystalline form.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. Here the reference explicitly teaches exactly what the compound is. The only difference is a characteristic about which the reference happens to be silent. See also Ex parte Anderson, 21 USPQ 2nd 1241 at 1251, discussion of Rejection E. There, the decision states, "There is ample precedent for shifting the burden to an applicant to reproduce a prior art product whose final structure or properties are, at least, in part determined by the precise process used in its manufacture." (page 1253). The "properties" branch of that statement applies here.

It is well settled that the PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical. An applicant's burden under these circumstances was described in *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) as follows:

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, or 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products (footnote omitted).

Applicants argued in their response of 2/28/2006 (now incorporated into the recent response) that the solvent was different, and about "Trituration", etc but these aregument are no longer being made.

Applicants now argue, "specific crystalline forms ... are not properties of famciclovir as physical properties such as melting point or boiling point." This cannot possibly be agreed with. The physical form that a compound takes is of course a "property". A physical property is not the same thing as an e.g. biological property, but a physical form is still a property. Are applicants seriously arguing that X-ray diffraction peaks for example are not a property? At any rate the reference "Chemistry Research Guide - Physical & Chemical Properties" is cited, which says, "CRC Handbook of Chemistry and Physics. 84th ed. (Annual) Premier source for property data. Provides information (in tabular format) for organic and inorganic compounds and the elements. Property data includes molecular weight (mw), physical form ...." This demonstrates that, as the word is commonly used,

property of a chemical compound includes physical form. The examiner just does not understand the basis for drawing the distinction here. For example, assuming that the compound is pure, the different melting points between two forms arises from there being two different crystalline forms (that is, different crystalline forms are expected to have different melting points). So it is not seen what basis there could possibly be for treating these two properties (crystalline habit, and melting point) differently.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The intention of claim 5 is unclear. The claim limitation in the claim now is already required by claim 1, according to the amended claim limitation.

The examiner is at a loss to understand the earlier traverse, and it may be that the claim language does not reflect applicants' intentions. Claim 1 already requires that all other forms, including form II, total less than 5%. Since

all forms combined must sum to less than 5%, the Form II must of necessity be less than 5%, which is all that claim 5 requires. If applicants disagree, they are invited to describe a material which falls within claim 1 but does not fall within claim 5. It may be that applicants intend "another Famciclovir crystalline form" to mean "each individual form", but that is not what the claim says. In other words, if a specimen actually had 4% Form II, 4% Form III and 4% Form IV, that would be thought of, and properly described as having 88% Form I, and 12% of "another Famciclovir crystalline form" since all of II, III and IV would be another form, and therefore would not fall within claim 1. In other words, the phase "another Famciclovir crystalline form" is a collective term denoting all forms which are not form I.

The most recent traverse adds nothing else. Applicants again are invited to describe a specific material which falls within claim 1 but does not fall within claim 5.

Claims 45-46 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims depend on a canceled claim.

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DMF/water, does not reasonably provide enablement for all other choices. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Brand teaches that the use of aqueous acetone gives famciclovir, not famciclovir hydrate. This then casts doubt on other aqueous solvents except for the aqueous DMF in the example.

The earlier traverses were unpersuasive. It is correct that Brand teaches that aqueous acetone gives famciclovir, but does not explicitly state that the product was Famciclovir and not famciclovir hydrate.

The examiner does not need rigorous proof. All that is needed is a reasonable basis to doubt. MPEP 2164.05 states, "Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary" that the claims are indeed enabled.

In response, applicants made two arguments. First, they state: "Especially because Brand used only ^{1}H-NMR and ^{13}C-NMR performed in solution, the NMR techniques used by Brand would not be expected to differentiate famciclovir from Famciclovir monohydrate."

This is simply untrue. First, Brand used elemental analysis to characterize the material, and all elements C, N and H were within proper error limits of the calculated for the non-hydrate. If this were actually the monohydrate, all three elements analysis would be outside the normal error ranges for the calculated percentage. Second, their reported melting point of 103-105°C is virtually identical, as noted by Brand, to the literature value of 102-103°C. By contrast, Harnden 1990 reports 87-95°C for the monohydrate.

Applicants second argument is: "One skilled in the art would recognize that one may need to use ^{13}C-solid-state NMR, preferably coupled with the use of high power proton decoupling, magic angle spinning and cross-polarization, to differentiate a crystalline substance from its hydrate." No evidence whatsoever is presented that such techniques are needed. Harnden 1990 as well as EP 885223 both report the monohydrate without resort to such techniques.

Thus, the reference says that it is Famciclovir, and it has the correct elemental analysis for Famciclovir, and it has the melting point for Famciclovir, and not the melting point for Famciclovir monohydrate, and hence there is every reason to assume that the reference has exactly what it says it has.

Applicants now argue that " Brand also did not provide details on the procedure used to do the elemental analysis." What procedure is used to do the elemental analysis is rarely given because it does not matter. Elemental analysis of organic materials, except in the most unusual cases, is entirely conventional and needs no explanation. There is no reason to think that Brand erred in his elemental analysis.

Applicants also state: "Claim 35 recites the use of water mixed with ethanol, DMF, DMA, acetonitrile, methanol, THF or isopropanol, which was demonstrated by Example 10 to succeed in making famciclovir monohydrate. Applicants contend that, regardless the disclosures of Brand, it would not be undue experimentation for one skilled in the art to prepare famciclovir monohydrate according to the process of claim 35."But Brand teaches that the use of aqueous acetone gives famciclovir, not famciclovir hydrate, and applicants' argument simply ignores this fact. MPEP 2164.05 states, "Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for

the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary" that the claims are indeed enabled. Brand provides the reasonable basis to doubt the statement in the specification, since Brandt does what the specification calls for and does not get the result that the specification sets forth.

Claims 45-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Where is this in the specification? The specification says that it can make Famciclovir itself of this level of purity, but nowhere does it say that the methanol or ethanol solvates have this level of purity.

The traverse is unpersuasive. Applicants refer to original claim 41, but that text is not in the specification. Further, claims 45-46 are not limited to Form III.

Claim Objections

Claim 40 improperly depends on both claim 39 and claim 8. Likewise claim 38.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Mark L. Berch/ whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Mark L. Berch/
Primary Examiner
Art Unit 1624

7/9/2007